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Original Article

Direct comparison of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome and restless legs syndrome

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ABSTRACT

Objective: Changes to transcranial magnetic stimulation (TMS) have been reported in obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS), although no direct comparison study is available. The aim of this new investigation is to assess and compare cortical excitability of OSAS and RLS patients using the same methodology and under the same experimental conditions.
Methods: Fourteen patients with OSAS and 12 with RLS were compared to 14 age-matched controls. All patients were untreated and had a severe degree of disease. Resting motor threshold (rMT), cortical silent period (CSP) and motor evoked potentials MEPs, as well as intracortical inhibition (ICI) and facilitation at interstimulus interval (ISI) of 3 and 10 ms, respectively, were explored from the right first dorsal interosseous muscle, during wakefulness.
Results: rMT was higher in OSAS than in RLS and controls. CSP was shorter in RLS only when compared to apneic patients, whereas it was similar between OSAS and controls. OSAS subjects exhibited slightly prolonged central motor conductivity, whereas MEP amplitude was smaller in both patient groups. The ICI ratio at ISI of 3 ms was decreased in RLS patients only.
Conclusions: Distinct changes of responses at TMS were found, probably connected with the different neurophysiological substrates underlying OSAS and RLS and could not be interpreted as a mere reflection of the effects of sleep architecture alteration. TMS can be considered an additional tool for the understanding of clinical and pathophysiological aspects of sleep disorders, and possibly for the evaluation of the effect of therapy.

1. Introduction

In the last years, several studies have been carried out to evaluate the neurophysiological pattern of cortical excitability to transcranial magnetic stimulation (TMS) in different sleep disorders, including obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS), based on evidence suggesting that there might be a transient modified global excitability of the cortical-spinal pathways in some sleep disorders[1–3]. A number of TMS studies have confirmed that the cortical silent period (CSP) was prolonged in OSAS patients [4–7], as a sign of an increase in gamma-aminobutyric acid (GABA)-B activity [8]. On the contrary, the dysfunction of subcortical structures in RLS might induce a cortical disinhibition [9] and an alteration in cortical plasticity [10], both of which are likely to be modulated by dopaminergic drugs [11,12]. However, although the findings from these reports seem to reveal substantial modifications of the cortical excitability compared to healthy good sleepers, the complexity and heterogeneity of sleep disorders, the relatively low number of investigations and the heterogeneity in the methods employed preclude a comprehensive understanding [13]. In particular, studies assessing whether these changes might be related to the underlying specific pathophysiological mechanisms of the different sleep disorders or they merely reflect a general effect of disturbed nocturnal sleep are missing. Moreover, to date no investigation aiming to a direct TMS comparison between OSAS and RLS patients has been conducted.

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TMS is a safe, non-invasive, and painless tool by which hypotheses regarding cortical excitability can be explored *in vivo* in humans. TMS allows the examination of the descending motor pathways, from the motor cortex down to the target muscles [14]. Different paradigms of stimulation can be applied to obtain direct measures of cortical excitability and can also be indirectly used to detect information regarding the function of various neurotransmission systems [15], providing insights into the complex pathophysiology of a number of psychiatric and neurological conditions. Several variables, such as the threshold to stimulation at rest (resting motor threshold, rMT), the motor evoked potentials (MEPs), the central motor conduction time (CMCT), and the CSP may be assessed by means of the single pulse technique. Additionally, the paired-pulse method allows the measurement of the intracortical inhibition (ICI) and intracortical facilitation (ICF) [16], that likely reflects the excitability of separate populations of intrinsic interneurons within the motor cortical areas [17].

The aim of this new study is to use these methods in order to detect any changes in the electrocortical excitability of patients with OSAS and RLS, both compared with age-matched controls, using the same methodology and TMS procedures for all participants as well as the same experimental conditions. Based on the heterogeneous data collected in our recent review on this matter [13], we hypothesized that changes to TMS in OSAS and RLS might represent disease-specific profiles rather than a general consequence of the sleep architecture alteration.

2. Methods

2.1. Subjects and assessment

Fourteen patients with OSAS (8 males and 6 females; mean age, 57.9 ± 6.02 years), 12 patients with RLS (4 males and 8 females; mean age, 61.7 ± 11.44) and 14 age-matched controls (5 males and 9 females; mean age, 64.4 ± 5.37 years) were consecutively recruited from the Sleep Research Centre of the "Oasi Institute for Research on Mental Retardation and Brain Aging", Troina (Italy). OSAS patients met the international diagnostic criteria [18], and their clinical-polysomnographic findings were concordant with a severe disease. Subjective sleepiness, assessed by the Epworth Sleepiness Scale (ESS), was relevant (average score 16 ± 4.96 S.D.) and nocturnal snoring was always reported; mean oxygen desaturation index (defined as the number of peripheral blood oxygen desaturation per hour >3% from baseline) was 59.9 ± 27.07 S.D. The participants with RLS fulfilled the latest International Restless Legs Syndrome Study Group diagnostic criteria [19], and their mean score at the International Restless Legs Syndrome Study Group rating scale [20] was compatible with a severe disease (25.3 ± 4.89 S.D.); their mean EES score was 12.8 ± 3.44 S.D.

The clinical-demographic evaluation included: age, gender, handedness, social and living conditions, general and neurological examinations, and co-morbidities. The right handedness of all individuals was checked with the Edinburgh Handedness Inventory [21]. None of the patients was treated, neither with continuous positive airway pressure (CPAP) nor with drugs for RLS.

Exclusion criteria were: age <18 years; history of major psychiatric illness or other neurological disorders (ie, Parkinson's disease, epilepsy, stroke, dementia, head trauma, multiple sclerosis, etc.); other sleep disorders, such as abnormal sleep–wake rhythm, insomnia, narcolepsy; previous treatment with CPAP or dopaminergic drugs; acute or chronic non-compensated medical illness, including chronic obstructive pulmonary disease; alcohol/illicit drug abuse; current intake of psychoactive medications or other drugs able to modulate cortical excitability (ie, steroids, beta-blockers, clonidine, etc.); Mini Mental State Examination [22] <24; any conditions precluding TMS execution. Electroencephalography (EEG) was performed to rule out predisposition to seizures. In addition, to rule out a possible spinal or peripheral contribution to the motor cortex excitability parameters, a routine conduction study of the right ulnar nerve, including the F-waves, was performed prior to the entry into the study; this was found to be normal in all patients.

The study was approved by the local Ethics Committee and all subjects gave their written informed consent prior to the study after full explanation of the procedure.

2.2. Transcranial magnetic stimulation

TMS was performed using a high-power Magstim 200^2 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). A 70 mm figure-of-eight coil was held over the motor cortex at the optimum scalp position to elicit MEPs in the contralateral First Dorsal Interosseous (FDI) muscle of the dominant hand. The rMT was defined as the lowest stimulus intensity able to elicit MEPs at rest of an amplitude >50 μV in at least 5 of 10 trials, according to the IFCN recommendation [23]. CMCT was calculated by subtracting the conduction time in peripheral nerves obtained by magnetic stimulation of the cervical root, from the MEP cortical latency obtained during moderate active muscle contraction, with a stimulus intensity set at 130% of the rMT. The CSP was determined with an approximately 50% of maximum tonic voluntary contraction of the FDI muscle, induced by single TMS pulses delivered at 130% of rMT. The mean CSP duration of 10 rectified trials was calculated.

Paired-pulse TMS was performed using a 70-mm figure-of-eight coil deriving pulses from a couple of Magstim 200^2 Stimulators, connected each other through a BiStim module (The Magstim Company, Whitland, Dyfed). The BiStim was connected to a CED Micro 1401 interface (Cambridge Electronic Design, Cambridge, UK) allowing stimulus generation and data capture. ICI and ICF were studied using the conditioning-test paradigm, applying two magnetic stimuli in rapid succession [16]. The conditioning stimulus was set at 80% of the subjects' rMT whereas the test stimulus was set at 130% of the rMT. The interstimulus intervals (ISIs) tested were 3 and 10 ms, given that maximum inhibitory effects are found at short ISIs (1–4 ms) whereas facilitatory effects can be observed at longer intervals (7–20 ms) [14]. Ten trials for both ISIs were recorded in a random way with an 8-s interval among each trial. Responses were expressed as the ratio between the MEP amplitude produced by paired stimulation and that produced by test stimulus alone. Data were collected on a computer and stored with software *ad hoc* for off-line analysis [24].

Electromyographic (EMG) activity was recorded with silver/silver-chloride disposable self-adhesive and self-conductive surface electrodes. The active electrode was placed over the muscular belly of the target muscle (FDI), the reference distally at the metacarpal-phalangeal joint of the index finger and the ground on the dorsal face of the wrist. All measurements were conducted while subjects were seated in a comfortable chair with continuous EMG monitoring to ensure either a constant level of muscular activity during tonic contraction or complete relaxation at rest. All procedures were performed in the same laboratory and situation, by the same operators for each subject during wakefulness and at the same time of the day (approximately 9–10 am).

The level of vigilance of apneic patients was constantly checked throughout the experiment and kept to an acceptable level by asking the subject the number of the current trial prior to the administration of each TMS pulse.

2.3. Statistical analysis

The comparison between the different parameters obtained in the three groups of subjects was carried out by means of the non-parametric Kruskal–Wallis ANOVA, followed by the Mann–Whitney

Table 1
Clinical features of the three groups of participants.

Variable	0-Controls		1-OSAS		2-RLS		Kruskal–Wallis ANOVA	Post-hoc Mann–Whitney test		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$p <$	0 *vs* 1	0 *vs* 2	1 *vs* 2
Age, years	64.4	5.37	57.9	6.02	61.7	11.44	NS			
MMSE	28.0	1.93	28.3	0.91	26.8	2.79	NS			
ESS	2.6	2.85	16.0	4.96	12.8	3.44	**0.000001**	**0.00001**	**0.000025**	NS
IRLS					25.3	4.89				
ODI			59.9	27.07						

Abbreviations: OSAS, obstructive sleep apnea syndrome; RLS, restless legs syndrome; S.D., standard deviation; NS, not significant; MMSE, Mini-mental state evaluation; ESS, Epworth sleepiness scale; IRLS, International Restless Leg Syndrome Study Group Severity Scale; ODI, oxygen desaturation index.
Numbers in bold are statistically significant differences.

test for independent data sets, used as a post-hoc analysis. The commercially available Statistica software package (StatSoft, Inc., 2001, STATISTICA data analysis software system, version 6; www.statsoft.com) was used. Differences were considered significant if $p < 0.05$.

3. Results

All participants completed the assessment and the TMS procedures without complaining any undesirable effect. Almost all OSAS patients tended to become drowsy during the execution of the TMS protocol because of their excessive sleepiness but none of them fell asleep and no particular solicitation was needed beyond the above-mentioned question on the number of the upcoming stimulus. Accordingly, we did not observe significant inter-trial variability of the MEPs amplitude for each apneic patient. Clinical-demographic characteristics of the participants are summarized in Table 1. Patients and controls were similar in terms of age, gender, social and living conditions, and global cognitive status. The general examination was unremarkable, except for overweight or obesity which was present in all OSAS patients; no focal neurological deficit or significant co-morbidity was evident. As expected, scores at the ESS were higher in patients than in controls and, among patients, they were slightly worse in the OSAS group.

As shown in Table 2, single pulse TMS-derived parameters showed relevant differences between the three groups. Motor threshold at rest was significantly higher in OSAS when compared with RLS and controls. CSP duration was significantly shorter in RLS when compared with OSAS patients, whereas it was similar between apneic patients and healthy subjects. The comparison of the characteristics of MEPs revealed that apneic patients exhibited both cortical latency and CMCT significantly prolonged, with respect to controls; similarly, CMCT of OSAS subjects was longer than in RLS patients. MEPs were smaller in amplitude in patients, without significant difference between the two groups. Finally, the amplitude ratio of the conditioned MEP at ISI 3 ms (ICI ratio) was significantly decreased in RLS patients compared to OSAS and controls, whereas the facilitatory component explored at ISI 10 ms was similar between patients and controls.

4. Discussion

The main finding of this study is the identification of different and possibly specific patterns of changes at TMS in patients with severe OSAS and RLS. These electrophysiological profiles might be the expression of different and still largely unknown pathophysiological substrates underlying these sleep disorders, rather than being a general consequence of sleep loss and instability on motor cortex excitability. In particular, recent studies exploring the impact of sleep fragmentation (SF) on cortical and subcortical excitability seem to provide a possible link between TMS data and the neurophysiologic substrates underlying the sleep disorders considered here, which are both characterized by markedly fragmented sleep. In an experimental model of SF, Scalise et al. [25] demonstrated that the known alterations of both central motor inhibition and movement-related cortical plasticity observed in RLS patients are not present after a night of fragmented sleep, suggesting that the TMS changes might be intrinsically related to the underlying disease per se, rather than being directly associated with the SF present in the RLS. In OSAS patients, the consequence of SF or chronic blood gas disturbance may underlie the lack of response to continuous theta burst stimulation, suggesting impaired long-term depression-like

Table 2
Parameters obtained at TMS in the three groups of participants.

TMS measure	0-Controls		1-OSAS		2-RLS		Kruskal–Wallis ANOVA	Post-hoc Mann–Whitney test		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$p<$	0 *vs* 1	0 *vs* 2	1 *vs* 2
rMT, %	43.8	5.62	51.0	6.29	44.7	9.02	**0.02**	**0.0054**	NS	NS
CSP, ms	71.8	25.42	73.8	12.28	60.6	7.09	**0.04**	NS	NS	**0.003**
MEPs										
sp-amplitude, mV	4.5	1.71	2.4	1.58	2.2	1.21	**0.001**	**0.002**	**0.001**	NS
cortical latency, ms	21.0	1.57	22.5	1.36	21.6	1.51	**0.03**	**0.015**	NS	NS
cervical latency, ms	14.4	0.91	14.4	1.08	14.6	1.14	NS			
pp-amplitude, mV	1.6	1.48	1.4	1.04	1.4	0.57	NS			
CMCT, ms	6.6	1.13	8.1	0.98	6.9	0.75	**0.0018**	**0.0014**	NS	**0.0064**
ICI, mV	0.7	0.69	0.9	1.09	1.4	0.98	NS			
ICF, mV	2.3	2.13	2.5	2.31	2.7	1.14	NS			
ICI ratio	4.0	3.89	3.7	3.93	1.6	1.23	**0.026**	NS	**0.007**	NS
ICF ratio	0.8	0.27	0.9	0.94	0.6	0.33	NS			

Abbreviations: TMS, Transcranial magnetic stimulation; OSAS, obstructive sleep apnea syndrome; RLS, restless legs syndrome; S.D., standard deviation; NS, not significant; rMT, resting motor threshold; CSP, cortical silent period; MEPs, motor evoked potentials; sp-amplitude, amplitude of MEPs elicited using single-pulse TMS; pp-amplitude, amplitude of MEPs elicited using paired-pulse TMS but produced by test stimulus alone; CMCT, central motor conduction time; ICI, intracortical inhibition; ICF, intracortical facilitation; ratio, ratio between the MEP amplitude produced by paired stimulation and that produced by test stimulus alone.
Numbers in bold are statistically significant differences.

neuroplasticity in these subjects [26]. Moreover, the effects of chronic SF have been also tested in adult male mice undergoing orbital platform SF [27]. The authors found that four weeks of SF impairs arousal responses to hypercapnia and reduces wake neuron projections and locus coeruleus neuronal excitability, supporting the concept that some effects of SF may contribute to impaired arousal responses in sleep apnea. Conversely, in agreement with the view of Allen et al. [28], a hyperarousal state might be present in RLS patients, who show increased EEG high frequencies during both the sleep onset period and the quiet wakefulness preceding sleep [29].

Based on these considerations, in the present study we found that apneic patients showed a global hypoexcitability of the stimulated cortex and a slower central motor conductivity, whereas RLS patients seem to exhibit an overall pattern of "disinhibition" of the motor cortex. These results confirm and extend some of the findings obtained by previous TMS studies in OSAS and RLS patients [13], although new data emerge from the present investigation, such as the lack of a longer CSP duration in apneic patients and the reduction of MEPs amplitude in both OSAS and RLS subjects.

The previous literature indicated that the most robust change in motor cortex function in patients with OSAS might be a prolonged CSP duration [4–7]; on the contrary, we did not observe significant differences in CSP between OSAS and controls. Interestingly, a recent investigation [26] assessing the long-interval ICI (LICI) as an alternative measure of GABA-B-mediated SICI, did not find significant difference between OSAS and controls, hypothesizing that this result may reflect methodological differences between the evaluation of LICI and CSP. In particular, the assessment of the CSP requires voluntary activation of the muscle, whereas LICI is assessed at rest. In patients with RLS, the results obtained from TMS studies are more contradictory probably due to the relatively small sample sizes and to the expected circadian distribution of the disorder. Current accepted mechanisms underlying the pathogenesis of RLS include a central dopamine dysfunction, a hyperexcitability of circuitry motor neurons, and an impairment of subcortical cerebral generators [13]. Based on the postulated mechanisms, the hypothesis of a shift in the balance toward more excitability and less inhibition has been proposed. Accordingly, as observed in other studies [3,30–32], we found the inhibitory components explored by TMS (CSP and ICI at 3 ms ISI) to be both reduced.

Conversely, a similarity between OSAS and RLS was found with decreased MEP amplitude in both groups of patients with respect to controls. It is worth to note that Civardi and colleagues [4] demonstrated that during non-REM stage 2 sleep, the average MEP amplitude was smaller and the MEP latency longer than in the awake state. During apneas, MEP size decreased and MEP latency further increased, suggesting a more enhanced depression of the cortical motor neuron activity. Because all of these TMS abnormalities were observed outside of the pharyngeal district, the authors pointed to a widespread dysfunction of the cortical-spinal system in OSAS, which becomes more evident during apneas [4]. While this finding in apneic patients might be interpreted as an additional index of cortical-spinal hypoexcitability together with the higher rMT value, the reason for small MEPs in our RLS patients is quite difficult to explain, also because previous studies have shown that the cortical-spinal conduction at TMS seems to be unaffected. As known, the reduced amplitude of MEPs is associated with a central motor conduction failure in many cases, but even in healthy people the size and latency of MEPs show great inter-individual and intra-individual variability, leading to a broad range of normal values [14]. Nevertheless, we cannot exclude a methodological interference on the measurement [10,33,34], given that the amplitude of the MEPs elicited using paired-pulse TMS but produced by test stimulus alone was comparable between patients and controls. Additionally, it might also be reasonable that we obtained this result because we have studied a severely affected subgroup of patients.

As for the MEP latency, a mild lengthening of CMCT is usually suggestive of degeneration of the fastest conducting cortical-motoneuronal fibres as well as increased desynchronization of cortical-motor neuron volleys [35], although we speculate that in apneic patients the underlying physiopathological mechanisms might be different. Accordingly, a recent paper [36] has shown that the activation of the cortical-bulbar pathway was reduced during NREM sleep in apneic patients, as demonstrated by increased MT and prolonged MEP latency recorded from the submentalis muscle. This diminished excitability is hypothesized to result from the combined effects of the thalamo-cortical system hyperpolarization and the modified reactivity to sensory inputs [37,38], leading to a prevailing tonic GABAergic and glycinergic inhibitory inputs to motor neurons [37], and thus probably resulting in a globally decreased excitability of the motor cortex and conductivity of the fastest conducting cortical-spinal projections.

There are some limitations to take into account when interpreting the findings of this study. First is the relatively small number of patients, although they were very homogeneous in demographics, clinical and sleep-related features. Second, the study was performed in the awake state, and thus in a different condition from sleep; however, as recently reported [9], nearly all studies, even the more recent ones, were performed during wakefulness, probably due to technical/procedural reasons. Third, the use of a hand muscle in RLS subjects might not be adequate, although some TMS measures have shown to be involved even when recording over hand muscles [31]; on the other hand, the known technical difficulties in MEPs recordings from lower limbs may affect the reproducibility of the results. Finally, all enrolled patients had severe conditions and therefore it was not possible to correlate the depicted changes at TMS with the different severity of the disease, as well as to capture eventual subtle electrocortical alterations in the mild disease stages; however, evaluating severely affected patients may allow to obtain more robust and reliable data.

Conflict of interest

The authors do not have any conflict of interest or sponsorship to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.08.016.

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